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## **Preventing venous thrombo-embolism after nonmajor orthopedic surgery**

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### **Abstract**

The venous thromboembolism risk is low to moderate in nonmajor orthopedic surgery. The literature is inconclusive. New emerging data are now available. The global patient risk has to be taken into account to determine the need for any prophylaxis

Venous thromboembolism (VTE) prophylaxis has been strongly recommended for more than 50 years after major orthopedic surgery such as, for instance, total hip replacement (THR) and knee replacement (TKR) (1-5). Hundreds of studies have demonstrated the high benefit/risk ratio of various antithrombotic agents when used after these high-risk procedures. At first in the 1950s' up to the 1970s', vitamin K antagonists have been used, and then, subcutaneous unfractionated heparin, low-molecular-weight heparins (LMWH), fondaparinux, hirudins and, more recently, direct oral anticoagulants (DOACs) have been successively prescribed in major orthopedic surgery, mainly THR and TKR, as a proof of concept, before being tested for the treatment of venous thromboembolism, or for the prevention of thromboembolic complications in atrial fibrillation patients. Aspirin has also been used extensively(6). International guidelines have provided high level recommendations for the post-operative prescription of all these agents in orthopedic surgery(3,4,7). Anesthesiologists and surgeons are well aware of these protocols which are part of their daily clinical practice. Indeed, all these antithrombotic agents may be responsible for an increase in the bleeding risk but, thanks to their efficacy, VTE (consisting of deep vein thrombosis [DVT] and pulmonary embolism [PE]) has almost disappeared in the orthopedic patients with less than 0.5% and 0.2% of events, respectively, at day 90 in the most recent cohorts(8,9). Therefore, prophylaxis has always been well implemented in major orthopedic surgery patients, and the related bleeding risk is well controlled.

Until now, this has never been the case for non-major orthopedic surgery (*Table 1*). Prophylaxis hasn't been systematically applied to these patients. North American guidelines (the American College of Chest Physicians [ACCP], for instance), always discouraged the use of VTE prophylaxis in these patients. However new data have appeared recently and

recommendations may change. We will here scrutinize the most recent literature and propose a few ideas to clarify this topic.

### **1 - A low VTE risk for non-major orthopedic procedures?**

The list of these procedures is quite long (~~Table 1~~). None of them is known to bear a very high VTE risk. However, this risk may vary from a procedure to another.

#### a) Femur, patella, tibia, Achilles, ankle and foot surgery

Few recent data are available. Without routine prophylaxis, the rate of symptomatic VTEs generally estimated to be below 1.5% during the VTE risk period (Table 2).

Femur, patella, tibia fracture: Using a retrospective health-system database study, Lowe et al. identified 11,313 adult trauma patients, among which some patients underwent an intramedullary nailing of the femoral (n= 2926) or tibial (n=1195) shaft (10). Chemo-prophylaxis with enoxaparin and mechanical prophylaxis were provided to all patients. The intra-hospital incidence of symptomatic VTE reached 1,33% and 0,34%, for the femur and the tibia, respectively. Post-discharge records were unavailable.

Warren et al. identified 120,521 lower extremity orthopaedic trauma patients operated between 2008 and 2016 using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database(11). The overall incidence of VTE over the study period was 1.7% for hip fractures, 2.4% for femur fractures, 0.9% for patella fractures, 1.1% in tibia and/or fibula fractures, and 0.6% in ankle fractures. Neither the type of VTE prophylaxis nor treatment/rehabilitation protocols were included as variables in the NSQIP database. VTE incidence didn't appear to decrease over the study period for femur, patella, tibia and/or fibula, and ankle fractures. However, information was too limited to provide a reliable picture of the VTE risk in this study.

Tibial osteotomy: Kim et al. included 133 patients in a prospective non-randomized comparative study (12). All patients underwent preoperative ultrasonography and computed tomography venography on postoperative day 5. Sixty-six patients received 2.5 mg fondaparinux for 5 days postoperatively, whereas a control group of 67 patients received a placebo. The overall incidence of DVT was 14.9% in the control group and 10.6% in the chemoprophylaxis group (NS). Proximal DVT occurred in only one patient in the control group, and there was no symptomatic DVT or pulmonary embolism in either group. Minor bleeding episodes occurred in four patients in the fondaparinux group. The authors concluded that routine chemoprophylaxis seemed to be unnecessary in this population with low VTE incidence.

Achilles repair: The three most important studies are summarized here. Patel et al. reviewed 1172 patients identified in a healthcare database who had Achilles tendon ruptures and did not routinely received anticoagulation (13). The incidence rate of symptomatic VTE at 3 months was 0.77% (0.43% DVT and 0.34% PE). Colak et al. recently published data from a retrospective analysis of 238 patients who underwent surgical treatment of Achilles tendon rupture(14). Despite LMWH prophylaxis for 20 days, the rate of symptomatic VTE was quite high, reaching 7.6% for DVT, and 1.7% for PE.

In contrast, Pedersen et al. reported the data of the nationwide Danish cohort study including 28,546 patients with Achilles Tendon Rupture (1997 to 2015) (15). These patients did not routinely receive treatment with anticoagulants. Only 389 (1.36%) patients were hospitalized with VTE during the follow-up period, 278 due to DVT and 138 due to PE.

Foot and Ankle: Richey et al. conducted a 2-part study: (1) a retrospective observational cohort study of 22,486 adults to calculate the overall incidence following foot and/or ankle surgery and (2) a retrospective matched case-control study to identify risk factors for

development of VTE post-surgery(16). The overall incidence of VTE was low (0.9%) leading the authors not to support routine prophylaxis for all patients.

Heijboer et al. matched 5,286 patients who received anticoagulant prophylaxis for below-the-knee surgery with 5,286 patients who did not receive anticoagulant prophylaxis(17). The risk of developing a VTE was significantly lower in patients who received anticoagulant prophylaxis than in those who did not (39 patients [0.7%] versus 99 patients [1.9%], respectively), with an odds ratio (OR) of 0.38 ( $p < 0.001$ ). Conversely, patients who received anti-coagulant prophylaxis had a significantly higher risk of developing a bleeding adverse event than those who did not (115 [2.2%] versus 55 [1.0%]; OR, 2.18,  $p < 0.001$ ).

Griffiths et al. compared the incidence of venous thromboembolism in 2,654 elective foot and ankle surgery consecutive patients with and without aspirin prophylaxis(18). The global incidence of VTE was very low: 0.42% (DVT, 0.27%; PE, 0.15%). There was no apparent protective effect against VTE associated with aspirin use. The authors concluded that routine chemoprophylaxis did not appear necessary for patients who are not in a high-risk group for VTE.

b) Knee arthroscopy (Table 3)

Diagnostic arthroscopy: Many cohorts and studies have evidenced a very low risk. Krych et al. reported a very low rate of symptomatic DVT and PE in a large cohort (n=12,595 patients) at a single institution(19). Chemoprophylaxis was not routinely used. An incidence of 0.30% for DVT, 0.06% for PE, and 0.34% for VTEs overall was observed. Hetsroni et al. reported an even larger cohort of 374,033 outpatients who underwent an arthroscopy(20). Only 117 PE (0.028%) were recorded.

In an open-label multicentre randomized trial, van Adrichem et al. compared an 8-days prophylaxis with low-molecular-weight heparin (LMWH) with no prophylaxis in 1543 patients undergoing an arthroscopy (the POT-KAST trial) (21). No significant difference was observed regarding VTE events (0.7% in the treatment group and in 0.4% in the control group) and major bleeding (0.1% in each group).

Camporese et al. allocated 241 patients to once-daily rivaroxaban (10 mg) or placebo for 7 days in a multicentre, double-blind randomized trial, the ERIKA trial(22). All patients underwent whole-leg ultrasonography at day 7(+1), or earlier if symptomatic. The primary efficacy outcome occurred in 0.8 % of the rivaroxaban group and in 6.1 % of the placebo group (p=0.03), with a majority of symptomatic distal VTE.

These two randomized controlled trials (RCTs) as six other smaller ones (overall 3218 patients) were included in a 2020 Cochrane database systematic review performed by Perrotta et al. (23). In the control group without LMWH prophylaxis, the rates of symptomatic DVT and PE reached 1.1% and 0.3%, respectively. Of note, LMWH didn't seem to bring any significant benefit with DVT and PE rates of 0.7% and 0.6%, respectively. No difference was observed in major bleeding (0.1% in each group).

*Anterior cruciate ligament (ACL) reconstruction:* Some of these patients may encounter a higher VTE risk. Gaskill et al. reported a total of 87 VTE events (0.53%) which occurred after 16,558 ACL reconstructions performed on 15,767 patients(24). DVT and PE were documented after 55 and 35 procedures, respectively, with 3 patients having both DVT and PE within the study period. This rate may appear relatively low.

Since this large cohort, Erickson et al. in a review of six other studies and 692 patients described an 8.4% rate of DVT after ACL reconstructions in patients without postoperative



thromboprophylaxis (2.3% were symptomatic), while the rate of symptomatic PE was 0.2% (25).

In a systematic review on this topic, Janssen et al. included 47 studies among which 11 studies focused on the VTE incidence (26). After ACL reconstruction without thromboprophylaxis, the incidence of DVT was 9.7%, including 2.1% were symptomatic. The incidence of pulmonary embolism was 0.1%.

Finally, Zhu et al. conducted a meta-analysis using data from eight randomized trials (4,113 patients) to compare LMWH with non-LMWH treatment in patients undergoing knee arthroscopy(27). Interestingly, they were able to compare simple, nonmajor procedures with procedures including ACL reconstructions. Compared with non-LMWH treatment, LMWH had no significant efficacy in preventing VTE in patients undergoing simple knee arthroscopic surgery but significantly increased the risk of major plus non-major bleeding events (BEs). On the other hand, LMWH had significant efficacy in preventing VTE for patients undergoing ACL reconstructions, without increasing the risk of BEs (major and all BEs).

As a summary, nonmajor surgical procedures globally bear a low VTE risk.

## **2 - Additional risk factors**

Most of the above studies question the benefit of prophylaxis except when additional risk factors are added on top of the surgical procedure.

In the Kim study (tibial osteotomy), the mean body mass index (BMI) was significantly higher in patients with than without DVT (12). In the Pedersen study (Achilles tendon surgery), hormonal contraception, previous VTE, older age group, and male sex increased the risk of VTE(15). In the Richey study (foot and ankle), obesity, history of VTE, use of hormone

replacement therapy, and postoperative non-weightbearing immobilization greater than 2 weeks, were significant risk factors(16). The risk of VTE increased significantly with 3 or more risk factors.

In the Krych study (arthroscopy), factors associated with an elevated risk of symptomatic postoperative VTEs included a history of malignancy, a history of VTEs, or the presence of more than 2 classic risk factors for VTEs(19). In the van Adrichem study (arthroscopy) the additional risk factors were older age, hormone use, and a family history of VTE(21). The same author had previously performed a large population-based case–control study in arthroscopy patients showing an increased risk for combinations with genetic and acquired risk factors including oral contraceptives, the factor V Leiden mutation, the factor II G20210A mutation, or non-O blood type(28).

Gaskill (arthroscopy with ACL reconstruction) identified an increased risk in patients aged >35 years with a history of nicotine use, anticoagulant use, concomitant high tibial osteotomy, or concomitant posterior cruciate ligament reconstruction(24). Jansen in his review pointed out common risk factors: female gender, > 30 years of age, complex or concomitant surgical procedures, prolonged immobilization and tourniquet time > 2 h(26).

Nemeth et al. reviewed VTE risk following lower-leg cast immobilization and knee arthroscopy(29). They propose to use risk assessment models to identify patients at risk and to decide on individualized thromboprophylactic therapy, rather than one standard treatment for all patients.

The most important additional risk factors are reported in Table 4. Using the Caprini score may also help in defining populations at higher risk for developing VTE(30).

### **3 – A meta-analysis and a subsequent very recent study**

Chapelle C. et al performed a meta-analysis of randomized controlled trials on the prevention of VTE with LMWH compared with placebo or no treatment in the nonmajor orthopaedic surgery setting all combined (31). Fourteen studies were included (4,726 patients). The weighted rate of major VTEs was estimated to be 2.9% without LMWH prophylaxis. Overall, a significant 68% reduction in the risk of major VTEs was observed with LMWH prophylaxis (relative risk [RR], 0.32;  $P < .001$ ). A nonsignificant 35% increase in the risk of major bleeding was observed in the LMWH prophylaxis group (RR, 1.35; 95% CI, 0.53 to 3.47). This meta-analysis showed a potential efficacy of LMWH in preventing thromboembolic events in patients with reduced mobility in the nonmajor orthopaedic setting. The rate of major venous thromboembolism (asymptomatic proximal deep vein thrombosis and any symptomatic venous thromboembolic event) without prophylaxis was 2.7% in patients with a distal lower limb injury and 3.2% in those undergoing knee arthroscopy. However, the authors stated that the decision of whether to implement LMWH prophylaxis should also take into account the risk of VTE in the absence of prophylaxis, the potential adverse effects of LMWH, and its cost.

Therefore, as the literature wasn't homogenous, as some patients appeared to benefit from VTE prophylaxis, and as LMWH prophylaxis was highly debated between North-American guidelines (not recommended) and European ones (standard of care in many European countries), we decided to build a large study assessing the benefit of a direct oral anticoagulant (rivaroxaban) as compared to the most popular LMWH (enoxaparin). Compared with enoxaparin, the factor Xa inhibitor rivaroxaban had been shown to reduce the composite of symptomatic venous thromboembolism and all-cause death after elective total knee or hip replacement surgery. Also, as an oral treatment, rivaroxaban is more convenient to patients than subcutaneous LMWH.

The PRONOMOS (PROphylaxis in NOn Major Orthopaedic Surgery) compared the effect of rivaroxaban with that of enoxaparin in preventing major venous thromboembolism in patients undergoing lower-limb nonmajor orthopedic surgery(32). The study was a multicentric (200 centers in 10 countries), randomized, double-blind, non-inferiority trial. Patients were included if they were adults and admitted to hospital to undergo nonmajor orthopedic surgery of the lower limbs and requiring thromboprophylaxis according to the investigator's judgement on the patient's venous thromboembolic risk. Types of surgery included Achilles' repair, knee surgery, tibial plateau, femur (excluding femoral head and neck fractures), tibial and ankle fractures and tibial osteotomy, tibial tuberosity transposition, arthrodesis of knee, ankle or hind foot, ligament repair of the knee with a planned immobilization or partial weight-bearing, ligament repair of the ankle, or any elective orthopedic lower limb surgery requiring thromboprophylaxis for more than 2 weeks. The primary efficacy outcome was the composite of symptomatic distal or proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism-related death during the treatment period, or asymptomatic proximal deep vein thrombosis at the end of treatment. The study was powered for non-inferiority, but a test for superiority was planned if non-inferiority was proven. A total of 3604 patients underwent randomization; 1809 patients were assigned to receive rivaroxaban and 1795 to receive enoxaparin. The primary outcome occurred in 4/1661 patients (0.24%) in the rivaroxaban group and in 18/1640 patients (1.10%) in the enoxaparin group (risk ratio 0.22, 95% confidence interval 0.07 to 0.65;  $P_{\text{superiority}}=0.002$ ). Bleeding rates in the intention-to-treat population did not differ between the rivaroxaban and enoxaparin groups (1.08% and 1.04%, respectively, for major plus nonmajor clinically relevant bleeding; 0.57% and 0.69% for major bleeding).

We acknowledge that a placebo arm was not present, and thus we don't know what the incidence of VTE would have in this group. However, the meta-analysis by Chapelle (31) had already almost answered this question.

Rivaroxaban proved more effective than enoxaparin in preventing venous thromboembolic events during a period of immobilization after nonmajor orthopedic surgery of the lower limbs. Still, no approval has been given by the FDA or the EMA, but we believe that nonmajor orthopedic surgery patients could benefit of an oral treatment rather than a subcutaneous injection.

## **Conclusion**

Nonmajor orthopedic surgery doesn't bear a high VTE risk, and prophylaxis could be omitted in some simple procedures. However, a patient case-by-case analysis has to be performed as soon as additional risk factors are present. In this regard, if a VTE prophylaxis is suggested, the better efficacy of rivaroxaban combined with the oral route of administration could lead to favor this treatment over LMWH.

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<b>Table 1 - Main types of nonmajor orthopedic surgery of the lower limb</b>
Hip arthroscopy
Femur fracture (excluding hip fracture)
Unicompartmental knee prosthesis
Ligament repair of the knee
Knee arthroscopy
Patella fracture
Tibial osteotomy
Tibia and/or fibula fracture
Tibial plateau
Tibial transposition
Arthrodesis of leg articulation
Ankle fracture
Ankle arthrodesis
Ligament repair of the ankle
Achilles' repair
Foot surgery
Material removal

**Table 2. Risk of symptomatic VTE after femur, patella, tibia, Achilles, ankle or foot surgery**

Study	Study design and period	No. patients	Outcome	Prophylaxis	Incidence rate
<b>Femur, patella, tibia fracture</b>					
Lowe et al (10)	American health-system database 2010-2017	4 121	Intra-hospital sympto. VTE	enoxaparin or mechanical for all patients	<b>1.33%</b> femur Fx <b>0.34%</b> tibia Fx
Warren et al (11)	NSQIP database (USA) 2008 and 2016	120 521	Sympto. VTE Day 30	NA	<b>1.7%</b> hip Fx <b>2.4%</b> femur Fx <b>0.9%</b> patella Fx <b>1.1%</b> tibia/fibula Fx <b>0.6%</b> ankle Fx
<b>Tibial osteotomy</b>					
Kim et al. (12)	Prospective cohort study 2012-2014	133	Sympto. VTE at day 5	Fondaparinux 2.5 mg or not	<b>0.015%</b> fondaparinux <b>0%</b> control
<b>Achilles repair</b>					
Patel et al. (13)	Healthcare database	1 172	Sympto. VTE at 3 mo.	No routine prophylaxis	<b>0.77%</b>
Colak et al. (14)	Retrospective cohort study 2006-2014	238	Sympto. VTE	Enoxaparin 20 days	<b>9.3%</b>
Pedersen et al. (15)	Nationwide Danish cohort study 1997-2015	28 546	Hospitalized VTE	No routine prophylaxis	<b>1.36%</b>
<b>Foot and Ankle</b>					
Richey et al. (16)	Retrospective cohort study 2008-2011	22 486	Sympto. VTE at 6 mo.	No routine prophylaxis	<b>0.9%</b>
Heijboer et al. (17)	Retrospective cohort study 2005-2015	10 572	Sympto. VTE	Anticoagulant and matched control	<b>0.7%</b> anticoagulant <b>1.9%</b> control
Griffiths et al. (18)	Retrospective cohort study 2003-2005	2 654	Sympto. VTE	Aspirin or not	<b>0.47%</b> aspirin <b>0.39%</b> control

VTE: venous thrombo-embolism; NSQIP: National Surgical Quality Improvement Program

NA: not available; Fx: fracture.

**Table 3. Risk of symptomatic VTE after knee arthroplasty**

Study	Study design and period	No. patients	Outcome	Prophylaxis	Incidence
<b>Diagnostic arthroscopy</b>					
Krych et al. (19)	Retrospective cohort study Single center 1988-2008	12 595	Sympto. VTE 4 wks	No routine prophylaxis	<b>0.34%</b> (0.25; 0.46)
Hetsroni et al. (20)	NY Health Database 1997-2006	374 033	Sympto. PE	NA	<b>0.028%</b>
van Adrichem et al. (21)	Open RCT (POT-KAST) 2012-2016	1 543	Sympto. VTE	LMWH or no LMWH 8 days	<b>0.7%</b> LMWH <b>0.4%</b> no LMWH
Camporese et al. (22)	Double-blind RCT (ERIKA) 2012-2014	241	Asympto VTE (US day 7)	rivaroxaban 10 mg or placebo 7 days	<b>0.8%</b> rivaroxaban <b>6.1%</b> placebo
Perrotta et al. (23).	Meta-analysis Cochrane (8 RCTs)	3 218	Sympto. VTE	LMWH vs no LMWH	<b>1.3%</b> LMWH <b>1.4%</b> no LMWH
<b>Anterior cruciate ligament (ACL) reconstruction</b>					
Gaskill et al. (24)	Military Healthcare System (USA) 2005-2011	15 767	Sympto. VTE 90 days	No prophylaxis	<b>0.53%</b> (0.42 ; 0.65)
Erickson et al. (25)	Review (6 studies)	690	Sympto. VTE	No prophylaxis	<b>2.5%</b>
Janssen et al. (26).	Review (11 studies)	30 368	Sympto. VTE	No prophylaxis	<b>2.1%</b>
Zhu et al. (27)	Meta-analysis (8 RCTs)			LMWH vs no LMWH	<b>1.23%</b> LMWH <b>1.96%</b> no LMWH

VTE: venous thrombo-embolism; PE: Pulmonary embolism; RCT: randomized controlled trial; US: ultrasonography; LMWH: low-molecular weight heparin; NA: not available.

<b>Table 4 – Main additional VTE risk factors</b>
Age > 60
Obesity (BMI > 30)
Active cancer
Current hormone therapy (contraceptive, Hormone replacement, tamoxifen)
Pregnant or immediately postpartum Extensive varicosities
Any serious medical comorbidity
VTE history
Known thrombophilia
Active smoker
Bedridden within the past 3 months
Full or semi-immobilization with a cast for more than two weeks